B; Egger, Matthias; Holzmann, David (2017). ***Outcome by treatment modality in sinonasal undifferentiated carcinoma (SNUC): A case-series, systematic review and meta-analysis***. Oral oncology, 75, S. 28-34. Elsevier

Abstract

OBJECTIVE: Sinonasal undifferentiated carcinoma (SNUC) is an aggressive malignancy first described by Frierson et al. in 1986. As the tumor is very rare, current treatment recommendations are based on institutional case reports. We thus felt the need to perform a comprehensive systematic review and meta-analysis to investigate how treatment modalities are associated with survival.

DESIGN: Case-series, systematic review and meta-analysis

METHODS: We searched the OvidMedline, OvidEmbase, Web of Science, Biosis, Scopus and the Cochrane Library database libraries. We extracted aggregate and individual patient data for statistical analysis. To study the association between treatment modalities and survival, we used random-effects meta-regression for the aggregate- and cox mixed-effects models.

RESULTS: 379 citations were found; 29 case series could be included in the final analysis, including a total number of 390 single patients (34.6% female). Median age at diagnosis was 52 years. 80.9% of patients presented with a T4 tumor and 16.0% with nodal metastasis at diagnosis. In individual patient data (IPD) meta-analysis, single modality (surgery alone or radiation alone) treatment was associated with reduced survival compared to double modality (surgery & radiation or chemoradiation) treatment (adjusted Hazard Ratio [aHR] 2.97, 95% ConfidenceInterval [1.41-6.27]) and compared to triple modality (surgery & radiation & chemotherapy) treatment (aHR 2.80 95%-CI 1.29-6.05 for triple vs. single modality). Triple modality treatment was not superior to double modality treatment. (aHR 1.06, 95%-CI 0.59-1.92).

CONCLUSION: Double and triple modality treatment are associated with improved survival over single modality but there is no evidence that triple modality is superior to double modality treatment.

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Introduction

Sinonasal undifferentiated carcinoma (SNUC) is a rare malignancy first described by Frierson *et al*.[1] in 1986. Frierson already recognized the aggressive behaviour of this malignancy, describing a median survival of 4 months in his series, where the vast majority of patients were treated with radiotherapy alone[1]. According to data from the Surveillance, Epidemiology, and End Results (SEER) database, the estimated incidence rate of SNUC is 0.02 per 100'000[2]. Histologically, SNUC is defined as a small round blue cell tumor that is immunohistochemically distinct from other sinonasal malignancies, such as lymphoma, mucosal melanoma, nasopharyngeal carcinoma, neuroendocrine carcinoma, and olfactory neuroblastoma[1]. Therefore, staining for leucocyte common antigen (LCA), S-100 protein, vimentin, in situ hybridization for Ebstein-Barr encoded RNA (EBER), synaptophysin and calretinin are typically negative while cytokeratins stain positive[3].

The management of SNUC is challenging as these tumors are located in areas difficult to reach, since they arise from the sinonasal cavity with frequent invasion of critical nearby structures such as the skull base or orbit. The traditional surgical management for those tumors is open craniofacial resection. A potential advantage of open surgery consists of approaching the tumor from around its healthy surrounding, dissecting towards the tumor, allowing en bloc resection and accurate margins assessment[4]. However, full open resection of gross disease can be linked to severe morbidity with uncertain benefit on survival. In recent years the advent of endoscopic sinus and skull base surgery for selected cases resulted in a dramatic decrease in morbidity, and might thus offer better quality of life in patients showing a poor prognosis[5]. Similarly to surgery for SNUC in general, the exact advantage of radiotherapy and chemotherapy in the primary or (neo-) adjuvant setting remains unclear. This lack of consensus can be explained by the rarity of the disease, which renders clinical trials difficult to perform in practice[6]. Consequently, current treatment regimens are based on small institutional case-series and differ widely[7]. Another issue is the management of the neck, as SNUC appears to show higher propensity to nodal metastasis than other sinonasal malignancies[7].

We therefore felt the need to perform a comprehensive systematic review and meta-analysis of the literature to investigate how treatment modalities are associated with survival and if elective treatment of the neck is justified. In addition, we present an institutional case-series of SNUC patients from the University Hospital Zurich.

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Data and Methods

Data

Institutional case series

We performed a retrospective study in SNUC patients treated at the Department for Otorhinolaryngology – Head and Neck Surgery of the University Hospital Zurich, Zurich, Switzerland. We examined charts to obtain detailed demographic and clinical data (sex, age, TNM stage, lymph node involvement, orbit and skull base invasion, treatment modalities, follow-up and recurrence). Data were anonymized according to ethical guidelines. We included only cases with histologically and immunohistochemically verified SNUC in the analysis. A Swiss Medical Association (FMH) board certified pathologist (KI) reviewed all cases to ensure the accuracy of the diagnosis. Staging was performed according to the American Joint Committee on Cancer (AJCC), TNM Staging for sinonasal cancer, 7th edition 2010[8]. All patients were presented at the local interdisciplinary tumor board and treatment recommendation was based on the available guidelines and literature at the time of the patients' accrual. This study was approved by the local Ethics committee (Protocol number 2016-0162).

Systematic review

We extracted information from all eligible publications using a standardised data extraction sheet and report the review according to PRISMA guidelines[9]. We searched for studies in the electronic databases OvidMedline, OvidEmbase, Web of Science, Biosis, Scopus, and the Cochrane Library using a strategy elaborated with the help of a medical librarian (Suppl. Table 1). In order not to miss any appropriate study, we did not apply any time or language limits in our search. The reference lists of review articles were screened for potentially eligible studies. Case reports were excluded.

The selection of studies involved an initial screening of the title and the abstract. In doubtful cases we obtained the full text. We entered articles in a data management software and eliminated the duplicates (Endnote 6®, Thompson Reuters Inc.). Two independent investigators (G.B.M. and D.V.) assessed information about participants (number of patients, study location(s), demographic variables), exposure and outcomes (treatment modality, recurrence, survival) and extracted it according to a detailed chart (Suppl. Table 2).

Statistical methods

Institutional Case series

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We describe the case series and calculated median, regional, distant metastasis-free, and disease-specific survival at 2 and 5 years using Kaplan-Meier methods.

Meta-analysis

To assess the association between treatment modality and survival time we analyzed the data from the literature search in two steps: first, we run a meta-analysis for the aggregate (summary) data of all publications. Then we performed an individual participant data (IPD) meta-analysis for those studies reporting data on individual patients[10]. For both analyses we included the data of our institutional case series as well.

For the aggregate meta-analysis we used 2-year-overall survival as outcome of interest, as it was the summary outcome measure most frequently reported at study level. If the 2-year survival was not reported for a study where IPD data could be extracted, we calculated it using the Kaplan-Meier method. The exposure was defined as the treatment combination composition of a study. For this we calculated for each study the percentage of patients in the treatment groups “palliative”, “surgery alone or radiotherapy alone”, "chemoradiation", “surgery & radiotherapy”, and “surgery & radiotherapy & chemotherapy”. As these percentages add up to 100% for each study, we applied the isometric log-ratio transformation for compositional data to the exposure. The outcome was logit-transformed for a more accurate model fit. To study the association between the treatment composition of a study and its reported 2-year overall survival, we first represented the data graphically by plotting the (transformed) 2-year overall survival versus the pairwise log-ratios of treatment compositions. In a second step, we fitted a random-effects meta-regression model (linear model).

For the IPD meta-analysis, we used disease-specific survival-time (time until disease-specific death of a patient) as outcome, as this was the outcome most frequently reported on individual patient level. Patients that did not die were censored at the end of their follow-up time. The exposure was defined as the treatment of individual patients and was grouped into six categories: "palliative", "radiotherapy alone", "surgery alone", "chemoradiation", "surgery & radiotherapy ", "surgery & radiotherapy & chemotherapy". First, we plotted Kaplan-Meier curves stratified for the six different treatment categories for descriptive statistics. Then we fitted a univariable cox-mixed effects regression model (maximum likelihood optimization) including a random intercept on study-level and “treatment group” as single covariate. In a second step we also added the covariates “N”, “M1”, “age”, “T4” to adjust for possible confounders. As the categorization into six different treatment groups might result in groups including very few patients and events we then built contrasts comparing the treatment combinations "palliative", “single modality” (that is surgery alone or radiotherapy

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alone), “double modality” (that is surgery & radiotherapy or chemoradiation), and “triple modality” (surgery & radiotherapy & chemotherapy).

Results of statistical analyses are presented as medians with interquartile ranges (IQRs) or ranges, percentages, means and hazard ratios (HRs) with 95%-confidence intervals (95%-CIs).
All analyses were carried out in SPSS® version 22.0.0 (IBM©, Armonk, NY, USA) and R version 3.2.3 (R Core Team, Vienna, Austria).

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Results

Institutional case series

Table 1 shows detailed numbers for the retrospective institutional case series. It included eleven patients treated between 2001 and 2014 with a median age at diagnosis of 51 years (IQR 45-57.5). All patients were of Caucasian origin. Five patients were smokers, while three reported frequent drinking of alcohol. Five patients exerted professions with potential dust and chemicals exposition (Table 1). Most common symptom at presentation was facial pain and nasal congestion. Hyposmia, diploplia and loss of vision were reported rarely (in one patient each). Eight patients had a clinical T4 at diagnosis. No patients had evidence of regional or distant metastasis at diagnosis. Invasion of the orbits, the dura, and the brain was seen in six, five, and two respectively.

Six patients were treated with open surgery, while two underwent endoscopic resection. All patients received postoperative adjuvant radiation with concomitant cisplatin, except for one patient that received adjuvant radiation only. One patient had induction chemotherapy with TPF (cisplatin, taxane, and 5FU) before surgery. Three patients were treated with primary radiation, two with concomitant chemotherapy (cisplatin), and one after induction chemotherapy by PF (cisplatin and 5FU). Intensity modulated radiotherapy (IMRT) was applied locally in all patients and to the neck nodes in 3 patients (Patient 4, 5, and 6). Mean radiation dose was 64.8 Gray (SE 1.31) locally and 57.6 Gray (SE 4.17) regionally. Median follow-up time in the cohort was 17 months (IQR 11.5-64). Median disease-specific survival time was 21.4 months.

Systematic review and meta-analysis

The search retrieved 379 references published until January 20th, 2014: 26 from Biosis, 1 from the Cochrane Library, 39 from OvidMedline, 186 from OvidEmbase, 47 from Scopus, and 80 from Web of Sciences. Crosschecking the references of the reviews led to the inclusion of one supplementary article. A search update which was done on December 14th, 2015, led to the inclusion of 3 more articles (Figure 1). Overall 29 studies were included (Table 2). Noteworthy, we had to exclude 7 case series, as the cases reported showed overlap with previously published case series (Suppl. Table 3). For 19 (67.9%) out of the 29 included studies we could extract IPD.

Study characteristics

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Including our case series, a total of 29 studies and 390 SNUC patients (34.6% female) were used for the meta-analysis. Median age at diagnosis was 52 years (range 36[11] – 69[12]). Most patients presented with a T4 tumor (80.9%), while 13.4% and 5.7% were T3 and T2/T1 tumors. Overall, an average of 16.0% of patients presented with nodal metastasis at diagnosis and 8.1% had evidence of distant metastasis. Overall, most patients had a triple modality treatment ("surgery & radiotherapy & chemotherapy" 36.2%), followed by double modality treatment ("chemoradiation" 26.0%, "surgery & radiotherapy" 16.9%) and single modality treatment ("surgery alone" or "radiotherapy alone" 16.0%). 5.0% of patients got palliative treatment only.

The cumulative local, regional, distant metastasis-free, disease-specific and overall survival were 70.4%, 73.1%, 75.5%, 55.4% and 51.5% at 2 years, and 69.6%, 79.4%, 63.4%, 37.4% and 36.4% at 5 years, respectively. Detailed results are shown in Suppl. Table 4.

Aggregate data meta-analysis

For the aggregate meta-analysis, we could use 20 out of the 29 studies (including 273 patients) because the other studies did not have complete reports on the 2-year overall survival or on the treatment composition (Table 3). The graphical representation of the data did not show any association between treatment compositions and survival (Suppl. Figure 1). It also revealed that there were very few studies that used all treatment modalities. As suspected graphically, when fitting the random effects meta-regression model, there was little evidence for a difference in 2-year overall survival related to treatment compositions (P=0.0789).

IPD meta-analysis

The 19 studies for which we could extract IPD included 232 patients. Out of these 19 studies, 17 studies (201 patients) were included in the descriptive analysis and univariable meta-regression because they had complete data on survival and treatment modality; 11 studies (135 patients) with complete data on all variables were included in the multivariable regression analysis (Table 3). The Kaplan-Meier curves for disease-specific survival stratified for treatment modalities are shown in Figure 2. The dual modality treatment "surgery & radiotherapy" seemed to achieve the best outcome, followed by triple modality treatment ("surgery & radiotherapy & chemotherapy") and "chemoradiation". As expected, patients treated as "palliative" had the worst outcome. Crude HRs (with 95% CIs and corresponding P-values) from univariable cox mixed-effects regression analysis and adjusted HRs (aHRs) from multivariable regression analysis (adjusted for T, N, M and

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age at diagnosis) comparing all treatment categories are shown in Table 4. Numerically, the aHRs for patients treated with "surgery & radiotherapy" was 3.97 (95% CI 1.27-12.42, *P*=0.018) compared to radiotherapy alone, and 3.92 (95% CI 1.19-12.92, *P*=0.025) when compared to surgery alone (Table 4). Similarly, patients treated with chemoradiation showed a better survival than patients treated with radiotherapy alone or surgery alone (aHR 2.55, 95% CI 1.12-5.80, *P*=0.037). In the unadjusted/univariable analysis, "surgery & radiotherapy" showed a trend towards superior outcome when compared to chemoradiation (HR 2.88, 95% CI 1.36-6.10, *P*=0.059). In the adjusted analysis, however, there was no statistical difference between "surgery & radiotherapy" and chemoradiation. The combination of "surgery & radiotherapy & chemotherapy" was not superior to "surgery & radiotherapy" and/or chemoradiation (Table 4).

Similar results could be observed comparing single, double and triple modality treatment (Table 5): patients treated with a single modality treatment were about 2.7 times more likely to die than patients treated with double modality treatment (HR 2.43, 95%-CI 1.42-4.18; aHR 2.97, 95%-CI 1.41-6.27) and about 2.3 times more likely to die than patients treated with triple modality (HR 1,83, 95%-CI 1.02-3.28; aHR 2,80, 95%-CI 1.29-6.05). There was no evidence that triple modality treatment was superior to dual modality treatment (HR [dual vs. triple modality] 0.75, 95%-CI 0.44-1.27; aHR 0.94, 95%-CI 0.52-1.70).

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Discussion

This study reports the clinical features and outcome of SNUC patients treated at a single institution and provides a systematic review and meta-analysis of the available literature on SNUC patients. We showed that combined treatment with surgery & radiotherapy or chemoradiation results in better disease-specific survival than surgery alone and radiotherapy alone. Interestingly, double modality treatment was always superior to single modality treatment but was not inferior to triple modality.

Our study had several limitations. The validity of our meta-analysis might be limited as it is questionable if the differences seen in meta-analyses of observational studies are really due to different treatments or due to differences not captured in the model[13]. Although we tried to adjust for different confounders like severity of the disease and general health at diagnosis by including the covariates T, N, M, and age into multivariable analyses, these variables might not be able to capture the entire state of health of a patient. Also, many factors such as type of radiotherapy, dose of radiotherapy, type of chemotherapeutic agents used could not be integrated in the meta-analysis because of the large heterogeneity between studies. Further, the status of the surgical margins, pathologic risk assessment (perineural and/or lymphovascular invasion) as well the impact of elective neck treatment on locoregional control could not be examined, as these were only very rarely reported. This might result in another bias, as one may consider to renounce to adjuvant therapy after obtaining satisfactory surgical clearance of the tumor. Of note, we do not consider the type of surgery (open vs. endoscopic) per se to have a prognostic impact, as surgery is meant to provide maximal clearance of the tumor, independently of the method used[5]. These limitations notwithstanding, being the largest meta-analysis so far with nearly 400 patients, and the first one to comply with the PRISMA statement[9], were important strengths of our study. This enabled us to provide several important insights on SNUC characteristics, management, and outcome.

First, we saw that almost two thirds of the SNUC patients were of male gender. Although SNUC has not been formally linked to professional exposure, the preponderance of male being affected by this disease suggests aetiological involvement of sexual hormones, smoking or occupational hazards[14]. Concerning the latter, exposure to several industrial compounds has been attributed to tumorigenesis in around 40% of all sinonasal cancers[15, 16]. Professionals working with wood have for example up to 500–900 times increased risk of developing sinonasal intestinal type adenocarcinoma[15]. For SNUC, the exact etiological agents have yet to

be identified. In our case-series, we didn't have any wood professionals, however five patients reported professional dust and chemical exposure (metallic hardware, cleaning products).

Second, in our analyses, chemoradiation was always superior to radiotherapy alone. This suggests, as previously reported[7], that SNUC are chemosensitive. Whether the better disease-specific survival obtained by adding chemotherapy during radiation is due to radiochemosensitization of the tumor (thus enhancing locoregional control) or systemic effect (thus preventing distant dissemination of the tumor) is yet to be answered. Importantly, we could not analyse separately the different types of chemotherapy due to the great heterogeneity among studies reported so far.

Third, we showed in multivariable analysis that patients with "surgery & radiotherapy" had better outcome than surgery alone. This suggest that combined treatment with surgical approach and postoperative radiotherapy should be offered, when surgical removal of gross disease is reasonably achievable.

Further, patients treated with "surgery & radiotherapy" showed a trend towards a better outcome over chemoradiation in univariable but not in multivariable analysis. This difference may be explained by the fact that patients with advanced local disease with invasion of the orbits, skull base and brain involvement were more likely to be offered chemoradiation than "surgery & radiotherapy", which resulted in an apparent poorer outcome in univariable, but not in multivariable (that is after adjusting for advanced T stage) analysis. Finally, although currently advocated by many authors[17], we failed to provide evidence for a survival advantage of patients undergoing trimodality treatment compared to double modality treatment.

Fourth, we reported an average of 16.0% of lymph node metastasis at initial presentation for SNUC patients. There were also 26.9% of patients demonstrating regional failure at 2 years. Likewise, 8.1% of patients present with distant metastasis at diagnosis while 24.5% of patients had distant failure at 2 years follow-up. Substantiating previous reports[7], these data emphasize the importance of regional and distant disease assessment in SNUC patients and may encourage surgeons and radio-oncologist towards elective treatment of the neck. For squamous cell carcinoma e.g. of the oral cavity, elective treatment of the neck is usually recommended if the risk of nodal metastasis exceeds 15%[18]. Although data is yet insufficient to determine

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which particular subgroup of SNUC patients are most likely to benefit from elective neck dissection, we believe that radiation field planning should include treatment of the neck. Furthermore, initial staging should always include assessment of distant disease. This meta-analysis shows that the most common distant sites are the lungs, followed by bone and liver.

In conclusion, this study shows that SNUC is an aggressive malignancy occurring mostly in men, with frequent nodal and distant metastasis, that is best treated, as demonstrated in multivariable analysis, by at least double modality treatment. When surgery is offered for a patient with SNUC, radiotherapy should always be considered as part of treatment planning in the postoperative setting. Second, the adjunct of chemotherapy to radiotherapy seems to provide a survival advantage as well. However, we were not able to show an advantage in survival for triple modality treatment compared to double modality treatment. The exact role of chemotherapy should be investigated in future studies.

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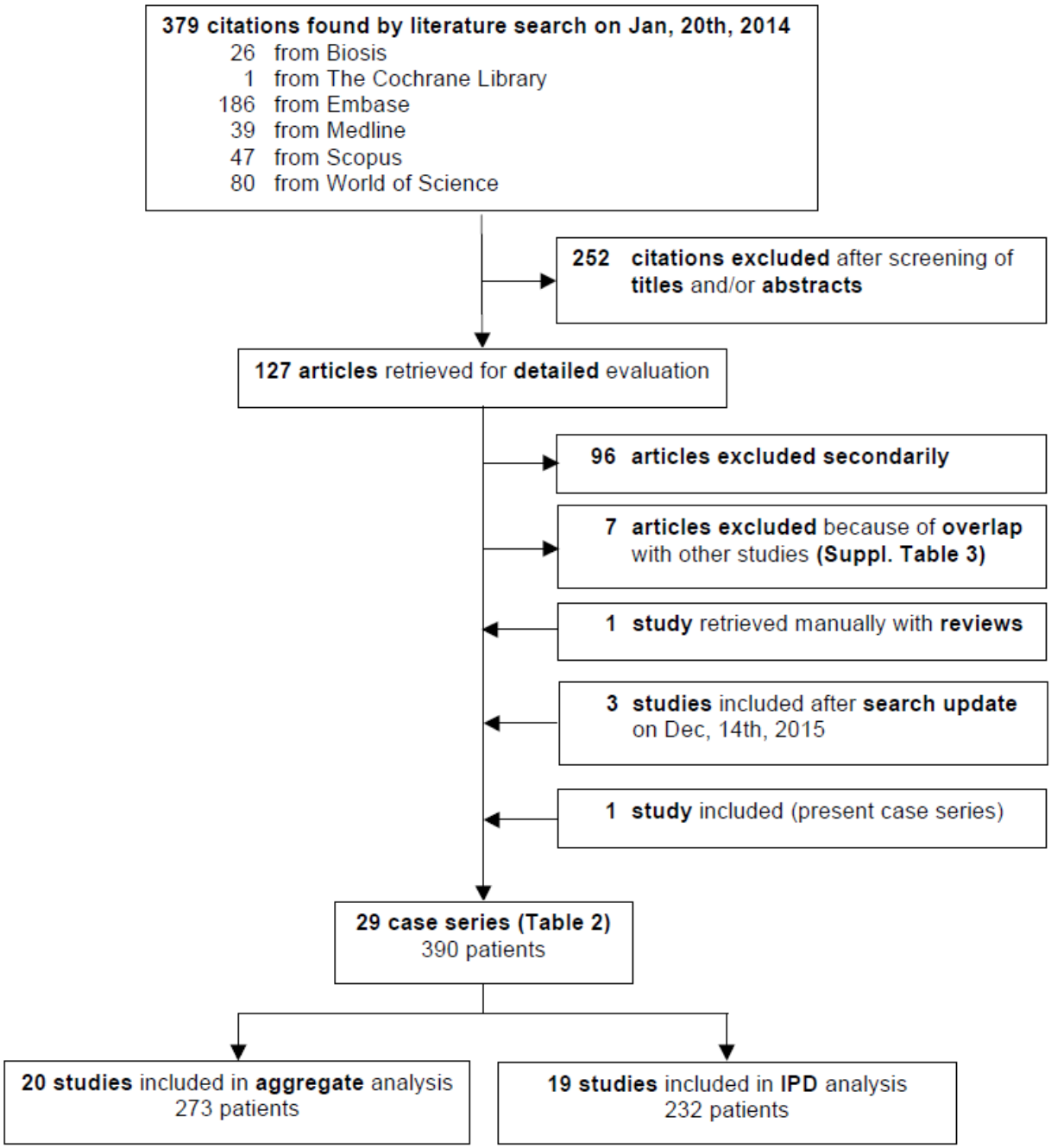

Figure 1: Flow-chart of study selection

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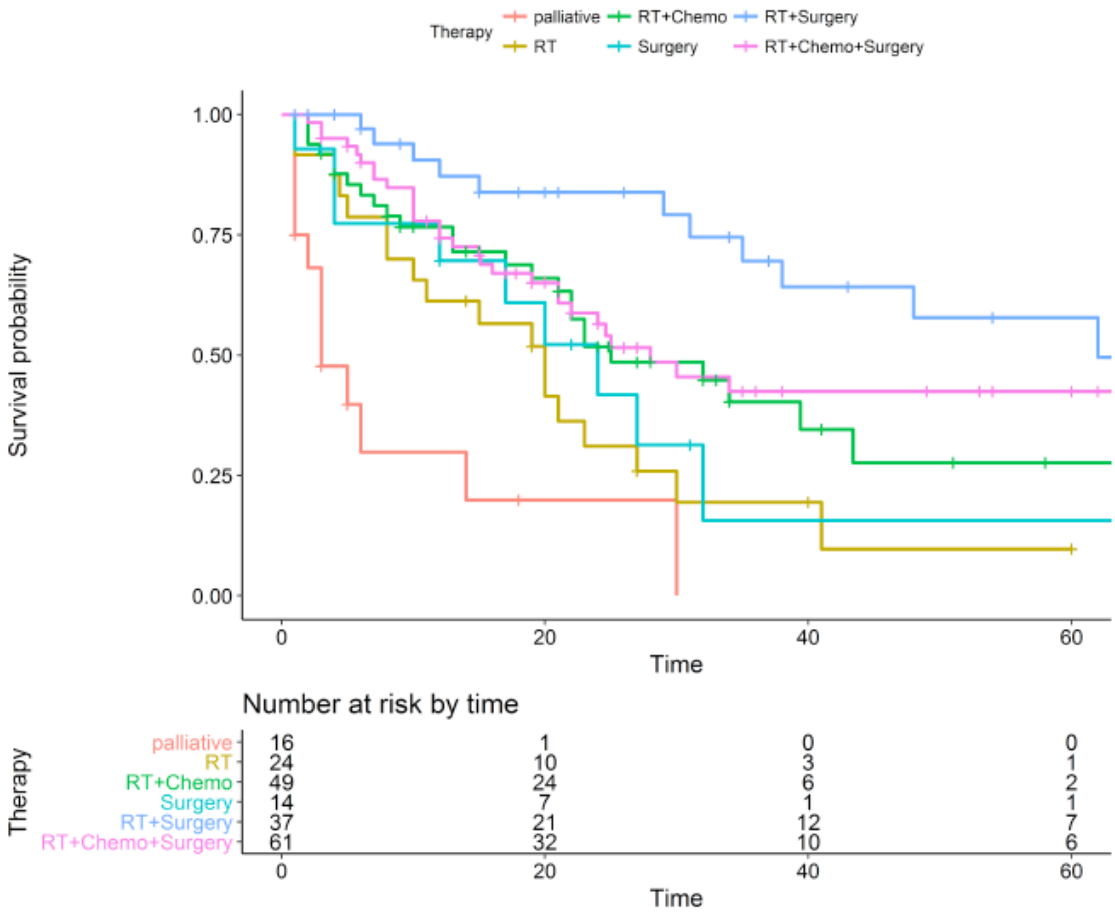

Figure 2: Kaplan-Meier curves demonstrating relative survival for each treatment category. Time expressed in months.

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Table 1: Baseline characteristics, treatment and outcome of SNUC patients treated at Zurich University Hospital

#	Age (y)	Sex	Employement	TNM	Surgery	IMRT (Gy)*	Chemotherapy †	Local recurrence (months)	Regional recurrence (months)	Distant metastasis (months, site ‡)	Death (months)	Follow-up (months)
1	58	M	Warehouseman	T4N0M0	None	68	Concomitant P	Y (2)	N	N	13	13
2	53	F	Office employee	T4N0M0	None	NA	Induction TF	N	N	N	2	2
3	51	M	Mechanic	T4N0M0	None	70	Concomitant P	N	N	Y (13, oss, hep)	17	17
4	33	M	Printer	T3N0M0	Endoscopic	70	Concomitant P	N	N	N	survived	22
5	57	M	Janitor	T4N0M0	Open	63	Concomitant P	Y (7)	N	Y (7, pulm, oss)	10	10
6	44	F	Bank employee	T3N0M0	Endoscopic	66	Concomitant P	N	N	N	survived	54
7	46	M	Traveling salesman	T4N0M0	Open	60	Concomitant P	N	N	N	survived	108
8	50	F	Bank employee	T2N0M0	Open	61.2	Induction TPF + Concomitant P	Y (89)	N	N	survived	99
9	65	M	Ambassador	T4N0M0	Open	59.4	Concomitant P	N	Y (12)	Y (12, pulm, oss)	13	13
10	69	M	Metallic hardware	T4N0M0	Open	62	Concomitant P	N	N	Y (19 pulm, oss)	74	74
11	25	M	Hotel industry	T4N0M0	Open	68.4	Concomitant P	Y (4)	Y (4)	Y (6, pulm, oss)	7	7

* IMRT: Intensity moduladed radiotherapy. Local doses shown. †: T: Taxane. P: Platin. F: 5-fluorouracil. ‡: oss: bone. hep: liver. pulm: lungs. NA: not available

Table 2: Overview of studies included in the metaanalysis (29 studies; 390 patients)

First author	Pub Year	Journal	Study University	City	State	Country	Number patients	Start year	End year
Frierson[1]	1986	Am J Surg Pathol	U of Virginia	Charlottesville	VA	USA	8	1942	1985
Levine[19]	1987	Laryngoscope	U of Virginia	Charlottesville	VA	USA	11	1975	1986
Gallo[20]	1993	Ear Nose Throat J	U of Florence	Florence	Toscany	Italy	13	1970	1990
Gorelick[11]	2000	Neurosurgery	U of Michigan	Ann Arbor	MI	USA	4	NA	NA
Miyamoto[21]	2000	Laryngoscope	U of Cincinnati	Cincinnati	IN	USA	14	1970	1999
Smith[22]	2000	Laryngoscope	Mount Sinai	New York	NY	USA	6	NA	NA
Heth[23]	2001	Skull Base	U of Iowa	Iowa City	IA	USA	9	1986	2001
Musy[24]	2002	Laryngoscope	U of Virginia	Charlottesville	VA	USA	15	1986	2000
Jeng[25]	2002	Am J Surg Pathol	National Taiwan	Taipei		Taiwan	36	NA	NA
Norleza[26]	2004	Med J Malaysia	U Kebangsaan	Kuala Lumpur		Malaysia	9	1999	2003
Rosenthal[27]	2004	Cancer	MD Anderson	Houston	TX	USA	16	1982	2002
Kim[28]	2004	Am J Otolaryngol	UCLA	Los Angeles	CA	USA	8	1995	2002
Rischin[29]	2004	Head Neck	Peter MacCallum CC	Melbourne		AUS	10	1990	2002
Kramer[30]	2004	J Otolaryngol	U of British Colombia	Vancouver	BC	Canada	4	1986	2001
Hoppe[31]	2006	Int J Radiat Oncol Biol Phys	Memorial Sloan Kettering CC	New York	NY	USA	4	1987	2005
Chen[32]	2007	Int J Radiat Oncol Biol Phys	Stanford	Stanford	CA	USA	21	1990	2004
Lin[33]	2009	Skull base	U of Michigan	Ann Arbor	MI	USA	19	1995	2008
Menon[34]	2010	Ind J Pathol Microbiol	Tata Memorial	Parel	Mumbai	India	5	2002	2007
O'Reilly[35]	2010	Laryngoscope	Mayo Clinic	Rochester	MN	USA	12	1980	2006
Revenaugh[36]	2011	Am J Otolaryngol	U Texas South Western	Dallas	TX	USA	13	2002	2009
Xu[37]	2013	J Otolaryngol Head Neck Surg	U of Alberta	Edmonton	AL	Canada	20	1986	2010

Al-Mangami[38]	2013	Eur Arch Otorhinolaryngol	Erasmus	Rotterdam		N'lands	21	1996	2010
Mourad[17]	2013	Am J Clin Oncol	Yeshiva University	New York	NY	USA	18	1997	2009
Yoshida[39]	2013	Am J Otolaryngol	Davis	Sacramento	CA	USA	16	1999	2009
van der Lann[12]	2013	Eur Arch Otorhinolaryngol	U Groningen	Groningen		N'lands	8	1980	2010
Christopherson[40]	2014	Am J Otolaryngol	U of Florida	Gainesville	FL	USA	23	1992	2010
Lopez[41]	2015	Rhinology	Asturias	Oviedo		Spain	17	2001	2013
Gray[42]	2015	Head Neck	Harvard	Boston	MA	USA	19	1995	2013
Morand	2017	*present cases series*	U of Zurich	Zurich		Switzer'd	11	2001	2014

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Table 3: Disease-specific survival for each treatment combination

Hazard ratio (95%-CI) *P value*	UNADJUSTED/UNIVARIABLE						ADJUSTED/MULTIVARIABLE (T, N, M, and age)					
	Palliative	RT alone	RT + Chemo	Surgery alone	Surgery + RT	Surgery + RT + Chemo	Palliative	RT alone	RT + Chemo	Surgery alone	Surgery + RT	Surgery + RT + Chemo
Palliative	**1**	**2.79 (1.30-6.0)** *0.0087*	**4.79 (2.2-10.46)** *0.000082*	**3.56 (1.44-8.79)** *0.0058*	**13.56 (5.63-32.68)** *0.000000062*	**5.31 (2.42-11.66)** *0.000032*	**1**	**2.67 (0.73-9.8)** *0.14*	**6.84 (2.22-21.10)** *0.00082*	**2.70 (0.69-10.56)** *0.15*	**10.60 (2.77-40.53)** *0.00056*	**7.24 (2.43-21.61)** *0.00039*
RT alone		**1**	**1.72 (0.87-3.39)** *0.12*	**1.28 (0.55-2.96)** *0.57*	**4.86 (2.17-10.90)** *0.00012*	**1.90 (0.97-3.75)** *0.063*		**1**	**2.56 (0.99-6.59)** *0.051*	**1.01 (0.32-3.21)** *0.98*	**3.97 (1.27-12.42)** *0.018*	**2.71 (1.07-6.84)** *0.035*
RT + Chemo			**1**	**0.74 (0.33-1.68)** *0.48*	**2.83 (1.34-5.98)** *0.0065*	**1.11 (0.62-1.97)** *0.73*			**1**	**0.40 (0.14-1.16)** *0.09*	**1.55 (0.58-4.13)** *0.38*	**1.06 (0.55-2.02)** *0.86*
Surgery alone				**1**	**3.81 (1.53-9.46)** *0.004*	**1.49 (0.67-3.31)** *0.33*				**1**	**3.92 (1.19-12.92)** *0.025*	**2.68 (0.97-7.42)** *0.058*
Surgery + RT					**1**	**0.39 (0.18-0.83)** *0.015*					**1**	**0.68 (0.26-1.76)** *0.43*
Surgery + RT + Chemo						**1**						**1**

RT= radiotherapy. Chemo= chemotherapy

Hazard Ratio = How much more likely is it to die of disease when you are in group *row* compared to group *column*

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Table 4: Disease-specific survival according to n-modality of treatment

Hazard ratio *P value*	UNADJUSTED/UNIVARIABLE Palliative	 Single modality	 Double modality	 Triple modality	ADJUSTED/MULTIVARIABLE (T/Kadish, N, M, and age) Palliative	 Single modality	 Double modality	 Triple modality
Palliative	**1**	**3.09** **(1.53-6.28)** *0.0018*	**7.53** **(3.67-15.47)** *0.000000038*	**5.66** **(2.63-12.17)** *0.000009*	**1**	**2.55** **(0.78-8.41)** *0.12*	**7.59** **(2.52-22.82)** *0.00031*	**7.14** **(2.41-21.17)** *0.00039*
Single modality		**1**	**2.43** **(1.42-4.18)** *0.0013*	**1.83** **(1.02-3.28)** *0.042*		**1**	**2.97** **(1.41-6.27)** *0.0043*	**2.80** **(1.29-6.05)** *0.009*
Double modality			**1**	**0.75** **(0.44-1.27)** *0.29*			**1**	**0.94** **(0.52-1.7)** *0.84*
Triple modality				**1**				**1**

Single modality: RT or surgery alone. Double modality: Combination of surgery & RT or RT & Chemo. Triple modality: Surgery & RT & Chemo
Hazard Ratio = How much more likely is it to die of disease when you are in group *row* compared to group *column*